EXHIBIT F

Expert Report re
Gynecare Prolift +M™ Pelvic Floor Repair System

I. Introduction

This report contains my opinions regarding the design, safety, and efficacy of the Gynecare Prolift +M™ Pelvic Floor Repair System, as well as the bases for my opinions. It also contains a summary of my qualifications, training, education, and experience, each of which forms a basis for my opinions. In preparation of this report, I have reviewed and considered published medical literature, literature reviews, journal articles, textbooks, and materials provided to me by counsel for Ethicon and Johnson & Johnson, including: company documents, reports of plaintiffs' experts and other company witness depositions on pelvic floor repair surgeries, including but not limited to that dealing with the Prolift™ system and Prolift +M™ system.

The materials that support my opinions are either identified in this report or contained on my reliance list. I hold all of the opinions set forth in this report to a reasonable degree of medical certainty. If I receive additional information prior to trial, I reserve the right to add to or change my opinions.

My C.V. includes a list of publications that I have authored over the past 15 years. A list of materials that I reviewed in forming my opinions is attached. I am currently being paid $500/hour to prepare a written report, $600/hour for depositions, and $725/hour for trial testimony.

II. Background

A. Education

I, Dr. Brian J. Flynn, attended the University of Rochester in Rochester, New York from 1987-1991. I graduated with a Bachelor of Science degree in Electrical Engineering with a concentration in Biomedical Engineering. I attended medical school from 1991-1995 at Temple University School of Medicine, Philadelphia, Pennsylvania and graduated with a Doctor of Medicine degree in May of 1995. I next attended Geisinger Health System, Danville, Pennsylvania for my internship and residency from 1995-2001. I completed a six-year residency in Urology. I then performed a fellowship in Reconstructive Urology, Urogynecology, and Urodynamics from July 2001-June 2002 at Duke University Medical Center under the directorship of Dr. George D. Webster. I then became a

staff faculty member at the University of Colorado School of Medicine in June 2002, where I have faculty since that time.

I became a diplomate of the American Board of Urology in March 2004 and became subspecialty certified in Female Pelvic Medicine and Reconstructive Surgery (FPMRS) in August 2014. I have had a Colorado Medical License continuously for the past 13 years. My hospital affiliations include University of Colorado Hospital, Denver Health Medical Center, Children's Hospital of Colorado, and Veteran's Administration Medical Center in Denver. My administrative activities include president-elect the South Central Section of the American Urological Association. I am the president-elect of the Rocky Mountain Urological Society. I have been the Director of a Fellowship in Reconstructive Urology at the University of Colorado School of Medicine since 2008. I am the Co-Practice Director of Women's Pelvic Health and Surgery at the University of Colorado Hospital since June 2013. I was the Assistant Residency Director of Urology at University of Colorado School of Medicine from July 2006-June 2010. I am an active member of the American Urological Association, South Central Section of the American Urological Association, Rocky Mountain Urological Society, Society of Genitourinary Reconstructive Surgeons, Society of Urodynamics, Female Pelvic Medicine & Urogenital Reconstruction, and International Urogynecological Association. This includes attendance at annual meetings and subscription to the associations' journals.

I review articles for the *Journal of Urology*, *International Urogynecology*, *Urology and Neurourology*, and *Urodynamics*. I have published scientific articles in peer review journals on male and female Reconstructive Urologic Surgery. I have authored instructional videos on the TVT Secur™, TVT Abbrevo™, as well as the Gynecare Prolift™ System and Prolift +M™ System. I have been invited to speak at a number of scientific meetings throughout the world on urogynecologic issues including incontinence, prolapse, neuromodulation, transvaginal mesh, and other female urology and urogynecology topics.

As a core faculty member of the University of Colorado School of Medicine Urology Division since 2002, I have instructed twenty-six residents on urinary incontinence and pelvic organ prolapse. Additionally, as the first founder and current fellowship director at the University of Colorado in pelvic medicine and reconstructive surgery, I have trained seven fellows in this specialty.

I spend 85% of my time in a clinical practice and 15% of my time in clinical research, teaching, administrative activities, medicolegal consultation, and quality improvement projects (e.g., improving bladder control and continence in multiple sclerosis patients).

I have extensive experience with transvaginal mesh and have published and presented numerous times on that topic. I am very familiar with the 2008 FDA Public Health Notification regarding transvaginal placement of surgical mesh and the FDA's 2011 update. In fact, the AUA (American Urological Association) asked me to write an update for practicing urologists on the implications of the FDA notification, as well as technical considerations of transvaginal pelvic reconstruction with polypropylene mesh. I have offered insight into prevention and management of mesh-related complications. I have proposed indications for mesh in stress urinary incontinence (SUI) and pelvic organ prolapse (POP) surgery. As a result of my education in engineering, I am certainly familiar with the biomechanical properties of polypropylene mesh. I have been invited to speak by many professional societies including the AUA, SUFU, and IUGA on the technical considerations and clinical considerations associated with transvaginal mesh.

B. Relevant Surgical Experience

I perform more than 400 surgical cases per year, primarily at the University of Colorado Hospital, and have done so for more than ten years. More than 50% of my practice involves Female Pelvic Medicine and Reconstructive Surgery. In the past 13 years, I have used polypropylene in pelvic floor repair of female SUI or prolapse in more than 1,000 cases. With respect to pelvic organ prolapse, I performed approximately 200 cases involving the Gynecare Prolift™ and Prolift +M System™ from 2006 until July 2012.

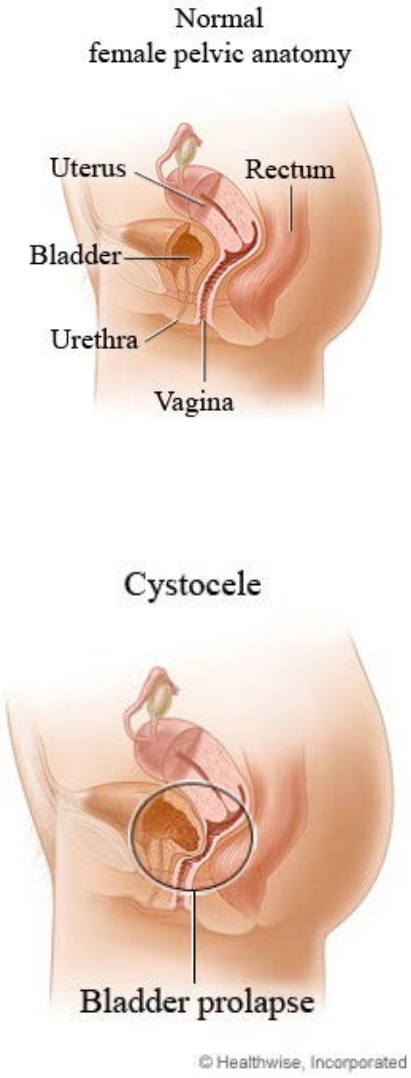
In 2012, I did my last Prolift +M case, but would have continued using Prolift and Prolift +M to this day if those products were available.

II. Incidence of Pelvic Organ Prolapse (POP), Description, Effect on Quality of Life

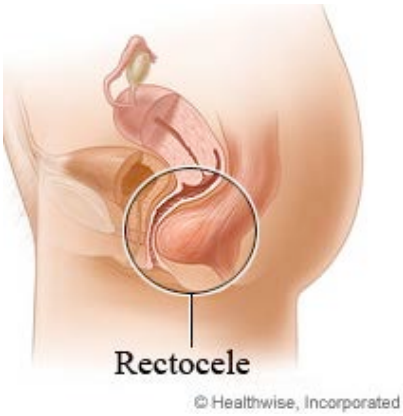
A. What Is Prolapse?

Pelvic organ prolapse (POP) occurs when a pelvic organ such as the bladder descends (prolapses) from its normal anatomic location in the vagina. It can be so severe that the organ prolapses outside of the vagina. POP can happen when the pelvic floor muscles that hold the pelvic organs in place are weakened or torn from aging, childbirth, or surgery. Many women will have pelvic organ prolapse. It can be uncomfortable or even painful.

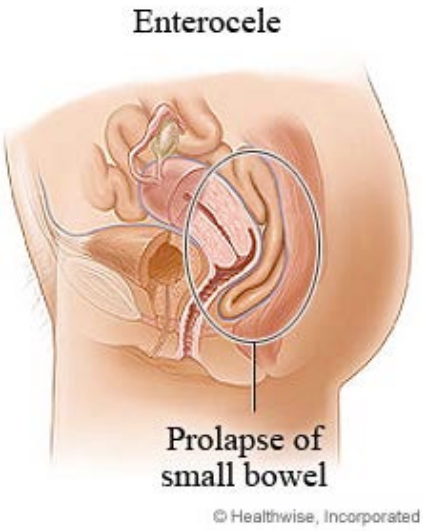
More than one pelvic organ can prolapse at the same time. Organs that can be involved when you have pelvic prolapse include the: bladder (cystocele), rectum (rectocele), small bowel (enterocele), and uterus (uterine prolapse).

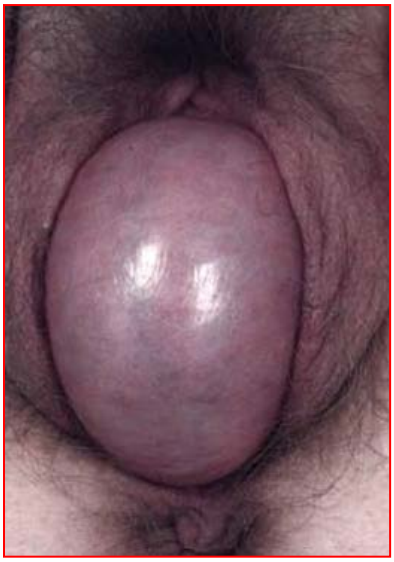


A bladder prolapse (cystocele) occurs when the tissues and muscles that hold the bladder in place are stretched or weakened. This causes the bladder to move from its natural position and press against the wall of the vagina, forming a bulge.



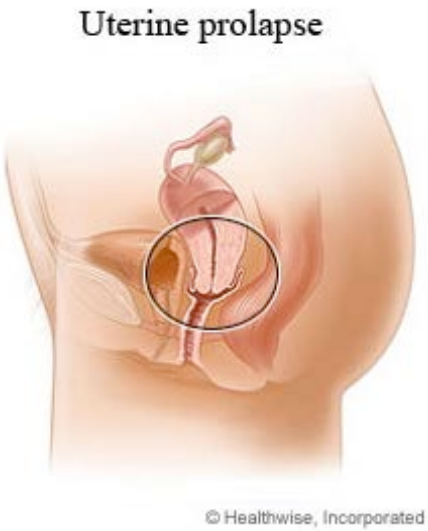
A rectocele occurs when the tissues and muscles that hold the end of the rectum in place are stretched or weakened. This can allow the rectum to press against the back wall of the vagina. Sometimes the tissues separating the two are so weak that the rectum bulges into the back wall of the vagina.





Vaginal Fault Prolapse with Enterocele

A small bowel prolapse (enterocele) occurs when the tissues and muscles that hold the small bowel in place are stretched or weakened. This can cause the small bowel to move from its natural position and press against the wall of the vagina.



A uterine prolapse occurs when a woman's pelvic muscles and ligaments become weak, causing the uterus to drop from its usual position. This allows the neck of the uterus (cervix) to bulge down into the vagina.

B. Etiology

POP is most often linked to strain during childbirth. During childbirth, pelvic floor muscles can get weak or stretched. If they do not recover, pelvic organ prolapse may develop. Surgery to remove your uterus (hysterectomy) can sometimes leave other organs in the pelvis with less support. Pelvic organ prolapse can be made worse by anything that puts pressure on the pelvis, such as obesity, lifting, chronic cough, and constipation. Older women are more likely to have pelvic organ prolapse. POP can be hereditary and related to connective tissue disorders.

C. POP Symptoms/Negative Effect on Quality of Life

The burden of urinary incontinence and prolapse on women is significant. POP affects almost half of all women over 50 years of age, with a lifetime prevalence of 30-50%. The estimated annual cost in the United States of POP is more than one billion dollars.[1]

Approximately 11% of American women will have an operation for incontinence and/or prolapse in their lifetime.[2] As many as 300,000 Pelvic floor

[1] Subak LL, et al., Cost of pelvic organ prolapse surgery in the United States. Obstet Gynecol 2001 Oct;98(4):646–651.
[2] Fialkow MF, et al., Lifetime risk of surgical management for pelvic organ prolapse or urinary incontinence. Int Urgogynecol J Pelvic Floor Dysfunct 2008 Mar;19(3):437–440.

reconstructive surgeries per year occur in the United States. As many as 29-40% of women will have the prolapse reoccur within three years of surgery.[3]

Symptoms of POP include: a sensation of pressure or fullness from pelvic organs pressing against the vaginal wall, a feeling that something is falling out of the vagina, a pulling sensation in the groin area, or pain in the lower back. POP may also cause incontinence or urinary frequency. POP may also cause vaginal or pelvic pain, or pain during sex, which is known as dyspareunia. Rectocele commonly results in severe constipation.

These symptoms may lead to social isolation and withdrawal from an active lifestyle. Patients withdraw from friends and family due to fear and embarrassment that POP and incontinence can cause. Patients often are afraid to leave home and do not go to family events, religious services, or sporting activities. They no longer perform physical exercise. Intimacy is often lost in a relationship due to painful sex that can result from POP. Hence, the burden on women is significant, and this leads to a desire by patients and physicians to find effective, durable treatment that would restore the normal pelvic anatomy and hence alleviate the symptoms that would then allow the patient to return to an active lifestyle.

III. Treatment Options for POP

Decisions on how to treat POP will be based on which pelvic organs have prolapsed and how bad the symptoms are. If the symptoms are mild, lifestyle changes may relieve many symptoms by adopting new, healthy habits. Pelvic floor exercises (called Kegels) that make the pelvic muscles stronger, weight loss, changes in diet, and avoidance of heavy lifting may help. A pessary is a vaginal support device that may help with the pain and pressure of pelvic organ prolapse. It is a removable device that holds the pelvic organs in place. In cases of severe prolapse, it may be hard to keep a pessary in place.

Surgery is another treatment option for serious symptoms of pelvic organ prolapse. Women will have surgery if:

- The prolapsed organ is causing significant pelvic pain;
- There are significant bladder or bowel problems;
- The prolapse is making it hard to do daily activities;
- Symptoms are affecting quality of life; or
- Prolapse makes it hard or impossible to have sex.

[3] Olsen AL, et al., Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997 Apr;89(4):501–506; Marchionni M, et al., True incidence of vaginal vault prolapse. Thirteen years of experience. J Reprod Med 1999 Aug;44(8):679–684.

Incontinence and prolapse surgery can be done using native tissue; what we refer to as traditional repairs. This includes using sutures to suspend the urethra, the bladder, or the vaginal apex, or plicating tissue over the organ to reduce the prolapse.

Surgery for POP can be performed by:

- Transvaginal approach;
- Open abdominal approach; or
- Laparoscopic/Laparoscopic-assisted robotic approach.

Other classifications include:

- Native tissue repair with or without permanent sutures;
- Surgery to close the opening of your vagina (colpocleisis);
- Surgery to remove the uterus (hysterectomy);
- Reinforced (augmented) repair with biological graft; and
- Reinforced repair with mesh graft with or without a "surgical kit."

A. Native Tissue Repairs

1. Anterior Vaginal Wall Native Tissue Repair

The purpose of anterior vaginal repair, or anterior colporrhaphy, is to plicate the vaginal fascia overlying the bladder (pubocervical fascia) to diminish the bladder and anterior vaginal protrusion. Anterior colporrhaphy is indicated especially for patients with a central vaginal defect. Several layers of interrupted delayed absorbable or permanent sutures are placed laterally on the pubocervical fascia in a mattress fashion. Excess vaginal mucosa is trimmed and the resulting vaginal mucosa is closed. Paravaginal defect repair may be performed laparoscopically, abdominally, or vaginally. In this procedure, the retropubic space of Retzius is entered to reattach the anterolateral vaginal sulcus with its overlying endopelvic fascia to the obturator internus and pubococcygeus muscles and fascia, thereby restoring the lateral vagina to its normal place of attachment.

2. Posterior Vaginal Wall Native Tissue Repair

Posterior vaginal repair (posterior colporrhaphy) is performed to repair the posterior vaginal defect—usually a rectocele. Traditionally, posterior colporrhaphy has been performed via a transvaginal approach and involves posterior colpoperineorrhaphy with levator ani muscle plication. In this surgery, the rectovaginal fascia is plicated in the midline, thus eliminating the posterior

vaginal protrusion, and the excess vaginal mucosa is excised and repaired with absorbable sutures.

Richardson introduced defect-specific—or site-specific—defect repair in 1972. It attempts to identify and repair specific areas of deficiency in the rectovaginal fascia. This type of repair does not attempt to plicate the levator ani fascia, and thus may be associated with a lower incidence of postoperative morbidity.

3. Apical Vaginal Prolapse and Uterine Prolapse, Native Tissue Repair

Many surgeons prefer vaginal surgery because the patient may have a shorter recovery time and it may take less intraoperative time compared with abdominal surgery. The most common vaginal procedures to suspend the prolapsed vaginal apex are sacrospinous ligament fixation (SSLF), modified McCall culdoplasty, iliococcygeus suspension, and high uterosacral ligament suspension.

Sacrospinous ligament fixation is usually performed on the patient's right side to avoid rectum and sigmoid colon injury. The ischial spine is palpated with the index finger and two pulley sutures of permanent or delayed absorbable material are placed through the sacrospinous ligament, two fingerbreadths medial to the ischial spine to avoid injury to the pudendal neurovascular bundle. The sacrospinous ligament pulley sutures are then attached to the vaginal vault and tied to pull up the vaginal cuff.

Vaginal obliterative procedures—partial (LeFort) colpocleisis and total colpocleisis—are indicated for patients who are not able to tolerate general anesthesia or long surgical procedures, and who are not contemplating future sexual activity. These procedures do not intend to correct an enterocele since they are both extraperitoneal procedures. Also, these procedures carry risk of postoperative de novo stress urinary incontinence, and thus a concomitant anti-incontinence procedure may be performed in at-risk patients prior to closing the vagina.

4. Surgical Outcome of Native Tissue Repairs

Native tissue repairs in the anterior compartment have a high failure rate (40-60%). According to a 2013 Cochrane review, Maher et al. reported that traditional anterior repair was associated with more anterior compartment prolapse on examination than for any polypropylene (permanent) mesh repair (RR 3.15, 95% CI 2.50 to 3.96). Awareness of prolapse was also higher after the anterior

native tissue repair as compared to polypropylene mesh repair (28% versus 18%, RR 1.57, 95% CI 1.18 to 2.07). Moreover, the anterior polypropylene mesh repair showed no difference in quality of life or de novo dyspareunia.[4]

Native tissue repairs fare better in the posterior compartment (5-25% failure rate). Barber in the OPTIMAL trial showed that success rate with USL and SSLF were approximately equal at 60%. This is much lower than the success rate of 70-90% generally reported in the literature for these procedures. Barber's results are consistent with other multicenter surgical trials where the treatment success rates were typically lower when combined by composite outcomes.[5] Posterior vaginal wall repair may be better than transanal repair. Adequately powered randomized, controlled clinical trials with blinding of assessors are urgently needed on a wide variety of issues, and they particularly need to include women's perceptions of prolapse symptoms. Although the success rate is high with respect to resolution of apical prolapse, new onset of prolapse may occur in the anterior compartment in as many as 8% of patients undergoing sacrospinous ligament fixation.[6] Therefore, it is common to prophylactically perform a concomitant anterior repair at the time of sacrospinous ligament fixation in efforts to avoid de novo prolapse in the anterior compartment.

Native tissue repairs often fail due to premature absorption of the sutures. Permanent sutures may break or pull through weakened degenerative tissue and this will lead to recurrent POP. As many as 40% of women will require a re-operation for recurrent prolapse.[7] Women often do not want to have the same surgery repeated, as they expect the same failed result. This leads to a feeling of despair and hopelessness. Hence, POP reoccurrence is a significant issue, as women will often not pursue further surgery and will have to learn how to live with POP. There are no longitudinal studies of native tissue repair with follow-up greater than five years. Most experts would agree that success rates of native tissue repair would be even lower if patients were followed for more than five years.

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[4] Maher C, et al., Surgical management of pelvic organ prolapse in women, Cochrane Review 2013.

[5] Barber MD, et al., Comparison of 2 Transvaginal Surgical Approaches and Perioperative Behavioral Therapy for Apical Vaginal Prolapse – The OPTIMAL Randomized Trial. J Am Med Assoc 2014;311(10):1023–1034.

[6] Cespedes RD, Anterior approach bilateral sacrospinous ligament fixation for vaginal vault prolapse. Urol 2000 Dec;4;56(6 Suppl 1):70–75.

[7] Olsen AL, et al., Epidemiology of surgically managed pelvic organ prolapse and urinary incontinence. Obstet Gynecol 1997 Apr;89(4):501–506; Marchionni M, et al., True incidence of vaginal vault prolapse. Thirteen years of experience. J Reprod Med 1999 Aug;44(8):679–684.

5. Complications of Native Tissue Repairs

Anterior colporrhaphy carries a risk of direct injury to the bladder, urethra, and ureters. Rates of ureteral damage are 0-2%. Injury to the urethra and the bladder neck is rare but may lead to intrinsic sphincteric deficiency. Voiding difficulty may occur after anterior colporrhaphy, and may require chronic catheterization. New-onset sexual dysfunction after anterior colporrhaphy occurs in up to 16% of women.[8]

Posterior colporrhaphy has a risk of rectal injury (1-3%) and dyspareunia (5-57%).[9]

Sacrospinous ligament fixation carries an approximate risk of buttock pain in 6%, de novo cystocele in 20%, new-onset stress urinary incontinence in 2.6%, and new-onset fecal incontinence in 4% of patients.

Uterosacral ligament suspension also carries a risk of ureteral injury as high as 11%.[10]

Both sacrospinous ligament fixation and uterosacral ligament suspension can lead to wound complications including suture erosion at reported rates of more than 15% in the OPTIMAL trial and up to more than 30% by others.[11] They can lead to dyspareunia as well, as shown in the Lowman 2008[12] study, which assessed rates of dyspareunia across numerous POP procedures:

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[8] Weber AM, et al., Anterior colporrhaphy: a randomized trial of three surgical techniques. Am J Obstet Gynecol 2001 Dec;185(6):1299–1304.

[9] Karram M and Maher C, Surgery for posterior vaginal wall prolapse. Int Urogynecol J 2013;24:1835–1841; Komesu YM, et al., Posterior repair and sexual function. Am J Obstet Gynecol 2007;197:101.e1–101.e6.

[10] Barber MD, et al., Bilateral uterosacral ligament vaginal vault suspension with site-specific endopelvic fascia defect repair for treatment of pelvic organ prolapse. Am J Obstet Gynecol 2000 Dec;183(6):1402–1410.

[11] Barber MD, et al., Comparison of 2 Transvaginal Surgical Approaches and Perioperative Behavioral Therapy for Apical Vaginal Prolapse – The OPTIMAL Randomized Trial. J Am Med Assoc 2014;311(10):1023–1034; Yazdany T, et al., Suture complications in a teaching institution among patients undergoing uterosacral ligament suspension with permanent braided suture. Int Urogynecol J 2010;21:813–818; Toglia MR and Fagan MJ, Suture erosion rates and long-term surgical outcomes in patients undergoing sacrospinous ligament suspension with braided polyester suture. Am J Obstet Gynecol 2008;198:600.e1–600.e4.

[12] Lowman JK, et al., Does the Prolift system cause dyspareunia? Am J Obstet Gynecol 2008;199:707.e1–707.e6.

TABLE 4
De novo dyspareunia after prolapse surgery

Dyspareunia	ASC N = 224 (148)[a] Handa et al[21]	SSLF N = 287 (106)[a] Maher et al[6]	USS N = 110 (34)[a] Silva et al[27]	APR N = 165 (81)[a] Weber et al[18]	Prolift N = 129 (57)[a]
Baseline (preop) dyspareunia (%)	40.5 (60/148)	Unknown	20.6 (7/34)	8.0 (6/81)	36.8 (21/57)
De novo (postop) dyspareunia (%)	14.5 (11/76)	36.1 (22/61)	25.9 (7/27)	19.0 (14/75)	16.7 (6/36)

[a] Number sexually active preop.

Lowman. Does the Prolift system cause dyspareunia? Am J Obstet Gynecol 2008.

In summary, native tissue repairs can cause numerous complications such as bleeding, infection, dyspareunia and pain, injury to surrounding organs including the bladder, bowel, rectum, or ureter. Nerve damage or entrapment can occur, leading to chronic groin or buttock pain. Native tissue repairs do not use transvaginal graft material, so they do avoid the risk of graft-related complications such as graft exposure. However, native tissue repairs often use permanent material such as sutures to plicate or suspend the prolapsed organ. These can lead to wound complications and suture erosion. For example, in a RCT of Prolift versus native tissue, there was a 15% rate of mesh exposure with Prolift and a 15% rate of suture erosion (apical Gore-Tex sutures) in the native tissue arm (n=5 for both).[13] Permanent sutures placed in the sacrospinous ligament should be done with caution, as they can cause pudendal nerve entrapment and chronic buttock pain. So, often the term "native tissue repair" is really a misnomer, and does not truly represent the entire concept of the repair.

B. Reinforced Repairs with Biological Graft (Allografts and Xenografts)

1. Use and Outcome

With advances in surgical biosciences, biological repairs evolved in the '70s and '80s. Graft material may be harvested from a cadaver such as fascia or dermis—known as an allograft—or using the same materials in animals such as a porcine or bovine graft—known as xenograft. These grafts are processed and packaged for distribution and use in multiple surgical sites including the pelvic floor. These grafts can be used as a sling in incontinence surgery, or they may be used to augment an anterior or posterior repair in prolapse surgery. They can also be used to suspend the apex of the vagina in sacrocolpopexy. Biomaterials seem to work by providing a scaffold for host tissue in-growth.

[13] Sokol AI, et al., One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. Am J Obstet Gynecol 2012 Jan;86:e1–e9.

2. Complications

Complications with reinforced repairs with biological grafts are similar to those seen in native tissue repair, and include injury to surrounding structures, dyspareunia, and suture exposure. In the systematic review by Abed et al. in 2011, exposure, wound complications, and dyspareunia were found to occur with biologics as well. There, 110 studies reported on erosions with an overall rate, by meta-analysis, of 10.3%, (95% CI, 9.7 – 10.9%; range, 0 – 29.7%; synthetic, 10.3%; biological, 10.1%); 16 studies reported on wound granulation for a rate of 7.8%, (95% CI, 6.4 – 9.5%; range, 0 – 19.1%; synthetic, 6.8%; biological, 9.1%); and dyspareunia was described in 70 studies for a rate of 9.1%, (95% CI, 8.2 – 10.0%; range, 0 – 66.7%; synthetic, 8.9%; biological, 9.6%).[14]

There are also unique complications with biografts such as tissue rejection and infectious disease transmission (Hepatitis, HIV, prions, etc.). Disease transmission can occur despite extensive steps to eliminate exposure. For instance, the risk of prions and HIV transmission is estimated to be about 1 in 1.7 million.[15] Tissue rejection leads to an exaggerated inflammatory response by the host. This leads to an inflamed, painful vaginal wall with vaginal discharge and pelvic pain/dyspareunia. There is also a significant expense associated with the processing, packaging, and storage of the graft material. Finally, there are religious and cultural reasons why many women simply object to the idea of having another human's or animal's tissue inside their vagina. For the above reasons, biologicals fell out of favor in the '90s and were replaced by synthetic material.

C. Abdominal Approach

1. Use and Outcome

The main abdominal operations performed for apical vaginal prolapse and uterine prolapse are abdominal sacrocolpopexy and total abdominal hysterectomy with high uterosacral ligament suspension. These operations allow fixation of the upper vagina or the uterus to the sacrum, with the help of grafts and sutures through the anterior sacral ligament (presacral fascia) at the level of the sacral promontory. The abdominal approach allows a higher vaginal fixation in the pelvis and provides durable repairs with an adequate vaginal length.

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[14] Abed H, et al., Incidence and management of graft erosion, wound granulation, and dyspareunia following vaginal prolapse repair with graft materials: a systematic review. Int Urogynecol J 2011 Jul;22(7):789–798.

[15] Flynn BJ, et al., Pubovaginal sling using allograft fascia lata versus autograft fascia for all types of SUI: 2-year minimum follow-up. J Urol 2002 Feb;167(2 Pt 1):608–612.

Sacrocolpopexy repair for apical vaginal prolapse is a procedure that may be performed by an open laparotomy or laparoscopic approach with or without robotic assistance. Grafts are placed from the vaginal cuff, or the amputated cervical stump, to the presacral fascia with permanent suture in a tension-free fashion. In 1962, Lane first described the use of graft material for sacrocolpopexy procedures (e.g., harvested fascia lata, abdominal fascia, cadaveric fascia lata, Marlex,™ Prolene,™ Gore-Tex,™ Mersilene,™ Vypro-II™) with variable success rates.

Sacrocolpopexy has superior outcomes to a variety of vaginal procedures including sacrospinous colpopexy, uterosacrocolpopexy, and transvaginal mesh. These benefits must be balanced against a longer operating time, longer time to return to activities of daily living, and increased cost of the abdominal approach.[16] In one study looking at outcomes of a group that had abdominal sacrocolpopexy plus Burch urethropexy and a group that had abdominal sacrocolpopexy alone, during seven years of follow-up, abdominal sacrocolpopexy failure rates increased in both groups. By year seven, the estimated probabilities of anatomic failure were 22-27% and symptom failure was 24-29%.[17] Abdominal sacrocolpopexy effectiveness should be balanced with long-term risks of mesh or suture erosion.[18]

Although the objective success rate of sacrocolpopexy is greater than sacrospinous ligament fixation (76% vs. 69%), sacrocolpopexy is associated with a longer operating time, a slower return to activities of daily living, and a greater cost.[19]

2. Complications

Abdominal sacrocolpopexy carries a risk of several complications, including new onset of stress urinary incontinence in up to 77%[20] and de novo dyspareunia in 5%.[21] Unfortunately, many large prospective randomized trials such as Nygaard in 2013 fail to report the incidence of dyspareunia. Vaginal mesh erosion rates vary from 6.9-27% with the probability of mesh erosion at 7 years of

[16] Maher C, et al., Surgical management of pelvic organ prolapse in women, Cochrane Review 2013.
[17] Nygaard I, et al., Long-term Outcomes Following Abdominal Sacrocolpopexy for Pelvic Organ Prolapse. J Am Med Assoc 2013 May;309(19):2016–2024.
[18] Nygaard I, et al., Long-term Outcomes Following Abdominal Sacrocolpopexy for Pelvic Organ Prolapse. J Am Med Assoc 2013 May;309(19):2016–2024.
[19] Maher C, et al., Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev 2004 Oct 18;(4):CD004014.
[20] Nygaard I, et al., Long-term Outcomes Following Abdominal Sacrocolpopexy for Pelvic Organ Prolapse. J Am Med Assoc 2013 May;309(19):2016–2024.
[21] Maher C, et al., Surgical management of pelvic organ prolapse in women. Cochrane Database Syst Rev 2004 Oct 18;(4):CD004014.

10.5% (95% CI, 6.8% to 16.1%).[22]

A review of more current studies from 2011 and 2012 suggest that transvaginal mesh placed by experienced mesh surgeons may have mesh erosion rates comparable to abdominally placed mesh.[23]

Unlike vaginal approaches, abdominal sacrocolpopexy has a significant risk of small bowel injury, ileus, hernia, and major hemorrhage due to injury to the middle sacral artery. There is also longer anesthesia time, convalescence, increased post-operative pain, and an unsightly abdominal scar when performed by an open approach. Laparoscopic and robotic approaches improve convalescence when compared to an open abdominal approach, but were not a widely available option in 2005 at the time Prolift was launched. Also, there is tremendous expense with laparoscopic and especially robotic-assisted approaches that many community and public hospitals cannot afford, and the learning curve has been reported to be very steep. Finally, since 2004, there have been training and credentialing issues with both laparoscopic and robotic surgery.

D. Mesh Evolution and Development

The use of surgical mesh began with abdominal hernia repair. Much of the technology, development, and lessons learned in this area inspired use and innovation in transvaginal surgery. In the 1950s, Lane first recognized the need for graft augmentation for prolapse to improve the disappointing surgical outcomes that existed at the time. In 1962, sacrocolpopexy began to be performed. In the 1960s, Moir introduced Mersilene mesh as sling material for stress urinary incontinence surgery. In 1970, Morgan reported on the use of Marlex polypropylene for SUI. In 1998, the TVT™ device, which uses Type 1 macroporous Prolene polypropylene, was introduced and quickly became the gold standard procedure for stress urinary incontinence. The material is excellent and the most suitable for use. Polypropylene became the preferred graft material for a reinforced pelvic floor repair in 2002 after the introduction of Gynemesh PS, which also uses macroporous Prolene polypropylene. The well-recognized advantages of a mesh-reinforced repair are the low failure rate in incontinence and prolapse surgery. Mesh grafts are especially valuable to patients with recurrent POP. However, the trade-off can be a mesh-related complication such as vaginal mesh exposure or extrusion, although wound complications and erosion also frequently occur with native tissue repair.

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[22] Nygaard I, et al., Long-term Outcomes Following Abdominal Sacrocolpopexy for Pelvic Organ Prolapse. J Am Med Assoc 2013 May;309(19):2016–2024.

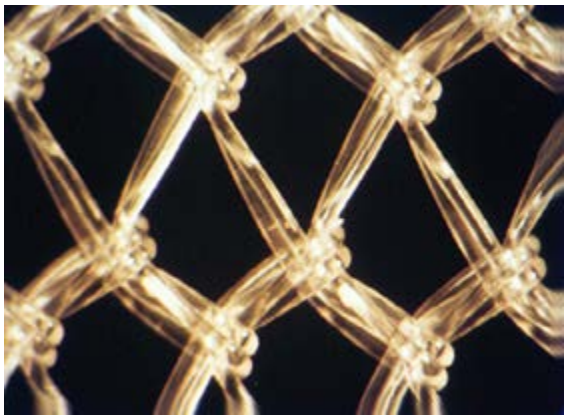
[23] Krlin RM, et al., Pro: the contemporary use of transvaginal mesh in surgery for pelvic organ prolapse. Curr Opin Urol 2012 Jul;22(4):282–286.

The Amid mesh classification published in 1997 for hernia mesh has been used to classify vaginal meshes as well. It primarily separates materials based on mesh pore size that has been related to infectious risk and tissue integration. In general, a pore size of >75 µm is considered macroporous and is desirable, as it allows passage of leukocytes and macrophages 9–20 µm in size. The problem with woven (as opposed to knitted) meshes and meshes with smaller pore sizes (< 75 µm) was that bacteria—which are very small (on the order of <1 micron in size)—can pass into the material, but the host's defense mechanisms, which are leukocytes and macrophages (9–20 µm in size), cannot. Interstices between multifilament fibers are also important, and those less than 10 µm may further perpetuate the problem. A pore size of >75 µm also allows capillary growth and the integration of tissue into the pores, prohibiting encapsulation and promoting support to the prolapsed organ.

Type 1 mesh is a macroporous (pore size > 75 µm), monofilamentous polypropylene mesh. Gynemesh PS™, the mesh used in the Prolift kit, is a type 1 mesh. The pore size of Gynemesh PS is about 2.5 mm or 2,500 µm, which easily accommodates the cells and small blood vessels needed to access the pores, promote tissue integration, and reduce the risk of infection. Type 1 meshes have been the standard mesh used in pelvic floor prolapse. Gynemesh PS is state of the art, and polypropylene monofilament macroporous mesh is the overwhelming choice of mesh for pelvic floor surgeons for the treatment of both prolapse and stress urinary incontinence. Prolift +M has a pore size of 3.5 mm post-absorption, and certainly is a monofilament lightweight type 1 mesh.

Type 2, 3, and 4 meshes such as Gore-Tex™ and Mersilene™, are microporous (pore size < 75 µm) multifilament meshes and are prone to infection. They are no longer used in transvaginal surgeries due to their lack of incorporation into the native tissue and their tendency to become infected. Their use in sacrocolpopexy has also been abandoned.

Type I: Knitted



Type II: Woven

Other mesh considerations for POP are that the mesh should be lightweight, flexible, and elastic. Large pore-size in meshes such as Prolift™ and Ultrapro enable a compliant, flexile scar that mimics natural tissue mobility.

Synthetic mesh has been shown to be superior to allografts, xenografts, and even autografts in terms of strength. Polypropylene mesh is constructed of monofilament material. Type 1 mesh like Gynemesh PS and Ultrapro produces an acute local inflammatory reaction and formation of fibrous tissue, but this decreases with time. Chronic inflammatory cells, which are commonly seen in vaginal tissues, may be seen near the mesh, but this is a normal foreign body response. The presence of chronic inflammatory cells is not indicative of an adverse biologic reaction or that the cells are actively trying to digest the foreign body. These cells can be in a quiescent state, essentially present but not activated. Moreover, mesh with large pore size (>75 µm) allows ingrowth of fibroblast, collagen, and blood vessels, and allows for macrophage and leukocyte infiltration and passage, thus decreasing the chance of mesh infection and mesh extrusion.

Gynemesh PS™ was noted to be even lighter than Gynemesh, with a weight of 44 g/m2 and again with greater elasticity. The polypropylene used in Gynemesh PS™ was the mesh used in the Gynecare Prolift™ kit. The next step for the industry was to produce even lighter weight, larger-pore meshes which, in theory, could decrease erosions and exposures, and result in decreased rates of dyspareunia or other complications.

Second generation transvaginal mesh kits composed of smaller, lighter weight, and mixed synthetic/partially absorbable mesh, as well as trocar-free delivery systems inserting directly into the obturator internus muscles and sacrospinous ligaments have evolved. Most of these new kits have been created

specifically for repair of anterior and apical prolapse.[24] For many years there has been interest in creating a partially absorbed mesh with a few goals: (1) provide additional stiffness at the implantation to improve graft handling and allow easier deployment to enable the mesh to more readily lie flat, (2) reduce the mesh load by decreasing the weight of the mesh while increasing the eventual pore size, and (3) reduce the polypropylene mesh load which would result in a milder inflammatory response compared to similar polypropylene constructs.

In theory, these design changes would further lessen the foreign body reaction that occurs with any graft material and reduce exposure or erosion rates and decrease the incidence of dyspareunia. In a study by Ozog, Prolift +M implants were noted to shrink by only 4.3%, without significant differences between the two directions of implantation.[25] My clinical experience is similar, in that I have not witnessed significant mesh contracture of Prolift +M mesh.

Second generation meshes include the Ethicon products Vypro and Ultrapro. Ultrapro is the mesh used in the Prolift +M device. These meshes have a lighter weight and a similar pore size at the time of implantation as Gynemesh PS, with a somewhat larger pore size post-absorption. A rationale for adopting a new, lighter-weight pelvic floor mesh with improved elastic properties and lower incidence of dyspareunia evolved.

Vypro is a mesh with 30% polypropylene and 70% polyglactin (PGA), resulting in higher elasticity and larger pores (Vypro; Ethicon, Hamburg, Germany). It was developed for incisional hernia repair.[26] This mesh proved to be favorable in both experimental and clinical studies, producing a reduced inflammatory reaction and better abdominal wall function. In consideration of the benefits of Vypro I mesh, a new mesh with temporarily increased stiffness was developed for inguinal tension-free repair and was known as Vypro II; (Ethicon). Vypro II is made of 50% PGA/50% polypropylene construct. Although the results of Vypro mesh for hernia repair were promising, they did not translate well to pelvic floor repair. Lim and colleagues noted that incorporating a Vypro II mesh overlay into a posterior colporrhaphy was associated with unacceptably high incidence of complications.[27]

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[24] Iglesia CB, Synthetic vaginal mesh for pelvic organ prolapse. Curr Opin Obstet Gynecol 2011 Oct;23(5):362-5.

[25] Ozog Y, et al., Persistence of polypropylene mesh anisotropy after implantation: an experimental study. BJOG 2011 Sep;118(1):1180–1185.

[26] Klinge U, et al., Influence of polyglactin-coating on functional and morphological parameters of polypropylene-mesh modifications for abdominal wall repair. Biomaterials 1999 Apr;20(7):613-23.

[27] Lim YN, et al., A long-term review of posterior colporrhaphy with Vypro 2 mesh. Int Urogynecol J Pelvic Floor Dysfunct. 2007 Sep;18(9):1053-7.

Ultrapro is a lightweight macroporous (>3 mm) monofilament polypropylene mesh. It contains an absorbable Monocryl component was added, which, in theory, would improve handling characteristics and ultimately reduce erosions.

When compared to 6 other polypropylene meshes, Ultrapro had the lowest (7.83 N) failure load and the highest relative elongations at mesh failure.[28] In fact, Shepherd and Moalli showed that Ultrapro is by far the least stiff mesh in the low stiffness range. All other prolapse meshes ranged from 7.9 to 80.4 times more stiff than Ultrapro.

The favorable biomechanical properties of Ultrapro led to the interest in seeing if this new mesh design could add to the success of Prolift. Prolift +M was the first pelvic floor mesh device designed with an absorbable component. It was composed of a 50-50 blend of absorbable poliglecaprone 25 (Monocryl) knitted with monofilament nonabsorbable polypropylene. In 3 months, the poliglecaprone-25 is absorbed, leaving less polypropylene in the vagina. The pore size following absorption increases from 2.5 to 3.5 mm. Prolift + M remains anisotropic after ingrowth into the host.[29] "Anisotropy means that the compliance is dependent on the direction of deformation."[30] The anisotropic properties of Prolift +M were designed to mimic that of the vaginal musculature—i.e., increased compliance in the transverse plane and limited compliance in the longitudinal direction. Before absorption, Prolift +M mesh weighs 57 g/m2. Full absorption occurs in 90-120, days resulting in a final weight of 31 g/m2, as opposed to the 45 g/m2 for Prolift. Prolift +M mesh was designed to have increased elasticity in the longitudinal direction as a result of its warp knitting and has larger pores compared with the original mesh to allow more tissue ingrowth. In 2008 Prolift +M™ was cleared by the FDA.

E. Prolift

1. Introduction of the Transvaginal Mesh Kit

The seven-year success of the TVT midurethral slings for management of stress urinary incontinence supported the use of polypropylene mesh for treatment of POP as well as the decades of use of mesh to treat POP. The polypropylene

[28] Shepherd JP, et al., Uniaxial biomechanical properties of seven different vaginally implanted meshes for pelvic organ prolapse. Int Urogynecol J 2012 May;23(5):613-20.
[29] Ozog Y, et al., Persistence of polypropylene mesh anisotropy after implantation: an experimental study. BJOG 2011 Sep;118(10):1180-1185.
[30] Ozog Y, et al., Persistence of polypropylene mesh anisotropy after implantation: an experimental study. BJOG 2011 Sep;118(10):1180-1185.

mesh and trocars like that used in TVT-O were partially incorporated into the use of the Prolift device. Specially designed devices are used to attach a preconfigured mesh to the pelvic sidewall, using the transobturator approach, or to the sacrospinous ligament. The transobturator approach entails the use of suspension arms passed through the obturator foramen, which suspend the graft through the arcus tendineus fascia pelvis ("ATFP"). Reported benefits of mesh kits over sutured mesh placement include decreased operative time, less extensive dissection, and more precise mesh tensioning.

The Prolift kit is a pre-cut piece of Type 1 Prolene polypropylene mesh with trocars used to insert the mesh. The trocars were useful in allowing fixation to structures that are ordinarily difficult to access. Critics will often state the tunneling device is placed blindly. However, surgeons that have actually used Prolift effectively in their practice know this is a misrepresentation of the facts. The tunneling trocar is placed under finger guidance (i.e., tactile guidance) as is done in other urogynecologic procedures, through reproducible and predictable anatomic landmarks. Placement of the trocar by tunneling through tissue is no different than placing other types of catheters in the human body such as placing an intravenous catheter, central line, or suprapubic cystotomy catheter.

Prolift was designed by a group of surgeons over four years to standardize a surgical technique for reinforced pelvic floor repair.[31] Standardization is an important step in improving and equalizing surgical outcomes achieved by pelvic floor surgeons. Standardization facilitates the ability of the technique to be safely replicated by other surgeons. The developers used well-known anatomic points that had previously been used for POP repair—the ATFP for paravaginal repair and sacrospinous ligament for sacrospinous ligament fixation. Both have been in use by pelvic floor surgeons for decades. The device was state of the art. The developers also assessed different meshes, and decided to use Gynemesh PS because of its characteristics and performance.

2. Prolift Pre-USA-Launch Clinical Data

Ethicon had the appropriate data to market and sell Prolift. Prior to Prolift being launched, mesh had been used in abdominal repairs since the 1950s and in sacrocolpopexy and stress urinary incontinence since the late 1960s. In the 1990s, surgeons began using mesh in vaginal prolapse repairs. Prolene sutures, which the mesh is essentially knitted from, have been in use by surgeons for decades, as well in various applications including prolapse and incontinence suspension repairs. Ethicon's Prolene mesh has been in use for over 40 years, and in the late 1990s, Ethicon manufactured and sold Prolene soft mesh for hernia use. Prolene Soft

[31] Berrocal J, et al., Conceptual advances in the surgical management of genital prolapse. J Gynecol Obstet Biol Reprod 2004;33:577–587.

mesh is the identical mesh used in Prolift. Prolene Soft mesh's extensive use in hernia repair demonstrated that it provided better success rates than native tissue repairs, and it was a bio-compatible mesh that had good properties for successfully treating hernia repairs, and that it adequately supported the herniated organs and tissue. This data was very helpful, as POP is essentially a hernia in the pelvic floor.

In 1998, Ethicon began manufacturing and selling TVT, which is a 1.1-cm-wide piece of macroporous Prolene polypropylene mesh for SUI repairs. These repairs occur transvaginally. This procedure has now become the gold standard for SUI repair. There are numerous studies with 5, 10, even up to 17 years of data showing that TVT, a macroporous Prolene polypropylene mesh, has very high success rates, compatibility, and very low complications. This information was very helpful in determining the role of polypropylene mesh for pelvic floor repair.

Gynemesh PS became available in 2002—this was the Prolene Soft mesh for use in the pelvic floor. A one-year study showed that Gynemesh PS implanted transvaginally had similar success rates to the gold standard of ASC; however, without the morbidity of an abdominal surgery. Further, the complication rates examined showed it to be a safe product. Gynemesh PS was further used from 2002 through 2005, and Ethicon continued to receive and review the reporting on the safety and efficacy of mesh used in the pelvic floor.

Nine accomplished French surgeons formed a study group to evaluate the potential for incorporating an adjustable delivery system into the grafted approach to overcome the inherent weakness in suture-fixated transvaginal grafts. The physicians engaged in one of the largest trials at that time to look at the safety and efficacy of the Prolift procedure with a TVM study on over 300 patients treated since 2002.[32] The study would grow and was reported in 2005 by Cosson et al. to include 687 patients, an unheard of number of patients at the time, and very large by even today's standards. No mesh kit had been studied nearly as much. This degree of study was revolutionary for POP mesh products and well beyond any POP industry standard. This study showed high success rates with minimal complications, similar to other transvaginal pelvic floor repairs. This study clearly showed that the benefits of a reinforced polypropylene mesh repair outweighed the risks. The TVM Group also assessed the use of Vypro, a larger-pore multifilament mesh, and determined that it was not suitable for use in pelvic floor kits.[33]

[32] Berrocal J, et al., Conceptual advances in the surgical management of genital prolapse. J Gynecol Obstet Biol Reprod 2004;33:577–587.

[33] Denis S, et al., Pelvic Organ Prolapse Treatment by the Vaginal Route Using a Vypro Composite Mesh: Preliminary Results About 106 Cases. ICS IUGA 2004;(Abs. 620).

Ethicon then sponsored a prospective trial that would look at the results of Prolift over a 1-, 3- and 5-year period. After approximately 6 months of data collection by Ethicon, Prolift was noted to be a safe and effective product in women.[34] Table 1 in the Jacquetin study also demonstrates that in multiple randomized controlled trials (RCTs) the use of trans-vaginal synthetic mesh or mesh kits was superior to traditional procedures for the treatment of POP in multiple studies.[35]

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Table 1 Randomised controlled trials comparing polypropylene mesh with traditional native vaginal tissue repairs

Reference	Total number patients	Follow up (months)	Compartment studied	Anatomic cure mesh (%)	Anatomic cure traditional (%)	*p*
Hiltunen et al. [9]	104	12	Anterior	93	62	<0.04
Sivaslioglu et al. [10]	90	12	Anterior	91	72	<0.05
Nieminen et al. [11]	105	24	Anterior	89	59	<0.05
Nguyen and Burchette [12]	75	12	Anterior	87	55	<0.05
Carey et al. [13]	139	12	Anterior Posterior	81	65.6	0.07
Nieminen et al. [14]	202	36	Anterior	87	59	<0.0001
Withagen et al. [15]	194	12	All	90	55	<0.001
Altman et al. [16]	389	12	Anterior	82	48	0.008
Sokol et al. [17]	65	12	All	38	30	0.45

As noted, the predicate TVM device was widely studied in Europe, and the data in over 600 patients was presented in 2005 at the International Continence Society (ICS) in Montreal, Canada, which was well-received.

This data is significant, as most complications occur within the first year. In summary, the multiple clinical trials, with over 687 women treated, showed that Prolift was a safe and effective procedure. Specifically, ranges of success were approximately 89% percent and exposure rates were approximately 13.3%, with dyspareunia almost non-existent.[36] Ethicon's decision that Prolift was safe and effective has been further confirmed with multiple clinical trials after launch, long-term studies, and my own clinical practice.

3. Prolift Post-Launch Clinical data

Prolift and Gynemesh PS have been the most extensively studied pelvic organ prolapse graft products. In this section, I will review this extensive data that clearly shows the superior success rates in mesh-augmented repairs when

[34] Jacquetin B, et al., Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int Urogynecol J 2013 Oct;24(10):1679–1686.
[35] Jacquetin B, et al., Total transvaginal mesh (TVM) technique for treatment of pelvic organ prolapse: a 5-year prospective follow-up study. Int Urogynecol J 2013 Oct;24(10):1679–1686.
[36] Cosson M, et al., Prolift (Mesh (Gynecare) for Pelvic Organ Prolapse Surgical Treatment Using the TVM Group Technique: A Retrospective Study of 687 Patients. ICS 2005; Abs. 121.

compared to native tissue. Also, this section will demonstrate that pelvic pain and dyspareunia improves in most patients following Prolift, and the incidence of de novo dyspareunia is no greater following Prolift when compared to native tissue. Much of the data is from multicenter randomized trials, which is one of the highest levels of scientific evidence.[37]

In a multicenter randomized prospective controlled study of 168 patients comparing sacrospinous fixation and transvaginal mesh, patients receiving transvaginal mesh were noted to have less recurrence of their prolapse (17%) when compared to native tissue repair (40%). Patients had significant improvements in quality of life as reflected by UIQ, CRAIQ, and POPIQ scores and sacrospinous fixation had lower improvement of bowel symptoms as reflected by the CRAIQ questionnaire. This was balanced against an exposure rate of 20.8%. There was not a statistically significant difference between sacrospinous ligament fixation and Prolift in dyspareunia or pelvic pain in this study.[38]

Da Silviera, in a multicenter randomized trial comparing native vaginal tissue repair and synthetic mesh repair for genital prolapse, demonstrated an 88% cure rate for Prolift versus 81% for traditional repair.
Moreover, Prolift patients had significantly better quality of life improvements (PQoL $p = 0.008$). There was not a statistically significant difference in the rate of dyspareunia between native tissue repairs (6%) and Prolift (3%), nor was there a statistically significant difference in the rate of pelvic pain between native tissue repairs (8.6%) and Prolift (2.3%). Finally, there was not a statistically significant difference in sexual function scores per QS-F questionnaire answers. Of the eighteen patients who developed a mesh exposure, fifteen of the patients had their erosions treated with topical estrogen and clinical observation.[39]

Svabik reported a significantly better cure rate of prolapse when comparing Prolift (97%) versus traditional repair (38%). There was minor mesh exposure at the 3-month follow up in the Prolift group in three (8%) cases; two of these were resected, while the third was asymptomatic and treated conservatively. There was no additional case of protrusion at the 1-year follow-up. There were five (15%) patients with vaginal blood spotting due to granulation tissue in the SSF group, all of whom were treated on an outpatient basis. Additionally, there was not a

[37] Oxford Levels of Evidence for Practitioners.
[38] Halaska M, et al., A multicenter, randomized, prospective, controlled study comparing sacrospinous fixation and transvaginal mesh in the treatment of posthysterectomy vaginal vault prolapse. Am J Obstet Gynecol 2012;207:301.e1–7.
[39] da Silveira S, et al., Multicenter, randomized trial comparing native vaginal tissue repair and synthetic mesh repair for genital prolapse surgical treatment. Int Urogynecol J 2015 Mar;26(3):335–342.

statistically significant difference in dyspareunia and PISQ scores between sacrospinous ligament fixation and Prolift.[40]

De Landsheere, in a retrospective trial of 524 patients from a single center with a median follow-up of 3 years, showed that the global reoperation rate was 11% (urinary incontinence 7%, mesh-related complications 4%, or prolapse recurrence 3%).[41] Notably, surgery due to symptomatic mesh retraction was very rare at 0.4% (2/524), and surgery due to mesh infection was only 0.2% (1/524).

In 2013, Dietz and Maher examined the effects of pelvic organ prolapse on sexual function. With regard to the anterior compartment, the use of mesh is associated with neither a worsening in sexual function by PISQ nor an increase in de novo dyspareunia compared with traditional anterior colporrhaphy. There is insufficient information to provide evidence-based recommendations on sexual function after new lightweight or absorbable meshes.[42] As shown in my report, in the Prolift RCTs which included treatment of the posterior compartment or total Prolift, there are no significant differences in dyspareunia or sexual function.

In a randomized trial, Withagen examined the effects of a trocar-guided mesh compared with conventional vaginal repair in patients with recurrent prolapse. Anatomic failure in the treated compartment was observed in 38 of 84 patients (45.2%) in the conventional group and in eight of 83 patients (9.6%) in the mesh group (P<.001). Subjective improvement was also seen. Pelvic pain and dyspareunia decreased at a similar rate at 1 year compared to baseline, in both groups. De novo dyspareunia was reported in 10% in the mesh group, and 8% in the Prolift group. There was a 16.9% rate of mesh exposure (n=14) with nine being asymptomatic. There were five exposures that required excision and they resolved.[43]

Sokol examined the objective and functional outcomes of randomized clinical trial of vaginal mesh for prolapse at 1-year. He noted that at 12 months, both groups had improvement of pelvic organ prolapse-quantification test points to similar recurrence rates. The quality of life improved and did not differ between

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[40] Svabik K, et al., Comparison of vaginal mesh repair with sacrospinous vaginal colpopexy in the management of vaginal vault prolapse after hysterectomy in patients with levator ani avulsion: a randomized controlled trial. Ultrasound Obstet Gynecol 2014 Apr;43(4):365–371.
[41] de Landsheere L, et al., Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up. Am J Obstet Gynecol 2012 Jan;206(1):83.e1–7.
[42] Dietz V and Maher C, Pelvic organ prolapse and sexual function. Int Urogynecol J 2013;24:1853–1857.
[43] Withagen MI, et al., Trocar-Guided Mesh Compared With Conventional Vaginal Repair in Recurrent Prolapse: A Randomized Controlled Trial. Obstet Gynecol 2011 Feb;117(2):242–250.

groups: 96% mesh versus 91% no-mesh subjects reported a cure of bulge symptoms. There was not a statistical difference between the no-mesh group (21%) and the Prolift group (10%) with respect to new-onset dyspareunia or sexual function. As noted earlier, there were an equal number of Prolift mesh exposures and suture erosions in the no-mesh subjects.[44]

In 2009, Carey reported the results of a randomized controlled trial comparing vaginal repair with Gynemesh PS mesh versus colporrhaphy for prolapse. Success at 1-year in the mesh group was 81% compared with 65% in the no mesh group. A high level of satisfaction with surgery and improvements in symptoms and quality-of-life data were observed in both groups. De novo dyspareunia was reported in 16% sexually active women in the mesh group versus 15% in the no mesh group. Most disturbing was the fact that two women in the no-mesh group required vaginoplasty for vaginal stenosis.[45]

In 2011, Altman published the results of a randomized trial of anterior colporrhaphy versus transvaginal mesh for pelvic organ prolapse in the New England Journal of Medicine. In this study of 389 evaluated at 1 year, the success rate was significantly more common in the women treated with transvaginal mesh repair (61%) than in those who underwent colporrhaphy (35%). More importantly, the mesh-based repair lasted longer. Surgical reintervention to correct mesh exposure during follow-up occurred in only 3% of patients in the mesh-repair group. There was not a statistically significant difference in pelvic or genital pain at 2 months or 12 months between the colporrhaphy and mesh groups. In fact PISQ-12 scores improved by 2% in native tissue repairs and 2.8% in Prolift repairs. Dyspareunia was reported “usually” or “always” by 2% of the women following colporrhaphy and by 7.3% after transvaginal mesh surgery, but the rates were not statistically significantly different. Finally, patient sexual satisfaction was 48% in the Prolift group compared to only 40% in the colporrhaphy group.[46]

Because of the high rate of baseline dyspareunia in patients with pelvic floor dysfunction, large, prospective, multicenter trials have been recommended by Lowman, et al. Lowman showed that POP repair, whether performed via an abdominal or vaginal approach, appears to have a high rate of associated

[44] Sokol AI, et al., One-year objective and functional outcomes of a randomized clinical trial of vaginal mesh for prolapse. Am J Obstet Gynecol 2012 Jan;86:e1–e9.
[45] Carey M, et al., Vaginal repair with mesh versus colporrhaphy for prolapse: a randomised controlled trial. Br J Obstet Gynecol 2009 Sep;116(10):1380–1386.
[46] Altman D, et al., Anterior Colporrhaphy versus Transvaginal Mesh for Pelvic-Organ Prolapse. N Engl J Med 2011;364:1826–1836.

dyspareunia.[47] The Prolift procedure has a de novo dyspareunia rate comparable to traditional repairs.

In summary, Prolift studies have more patients and longer follow-up than native tissue repair. The clinical data is clear that Prolift can be performed safely and effectively with results that approach the gold standard procedure abdominal sacrocolpopexy with Prolene mesh. Moreover, these randomized controlled trials show that the vast majority of patients do not have dyspareunia or unprovoked pelvic pain after undergoing transvaginal mesh surgery. It is also important to note just how prevalent pelvic pain and dyspareunia are in women with prolapse who have never had any pelvic surgery. Many of these women have improvement in their pelvic pain as a result of Prolift effectively resolving their prolapse. As with all prolapse surgeries, wound complications such as suture erosion and granulation tissue are known risks that can occur in native tissue procedures, while mesh exposure is a known risk of using mesh whether transvaginally or abdominally.

F. Prolift +M

1. Introduction and Clinical Data

In 2011, Milani and colleagues from the TVM group aimed to evaluate anatomic and functional outcomes at 1-year following trocar-guided transvaginal prolapse repair using a partially absorbable mesh (Prolift +M).[48] This was a prospective multicenter cohort study at 11 international sites, 127 patients with pelvic organ prolapse stage III underwent Prolift +M. The success rate was 77.4%. Significant improvements in bother, quality of life, and sexual function were detected at 3 months and 1 year compared with baseline. At 1-year after surgery, 86.2% of patients reported that their prolapse situation to be “much better.” Mesh exposure rate was 10.2% and rate of de novo dyspareunia 2% at 1 year, which is comparable to reported rates with Prolift, but low compared to native tissue repairs (14-36%).[49] Bhatia and colleagues, in 2012, reported on their study comparing sexual function outcomes one year after Prolift repair versus Prolift +M repair, and found that there was no significant difference between the two groups’

[47] Lowman JK, et al., Does the Prolift system cause dyspareunia? Am J Obstet Gynecol 2008;199:707.e1–707.e6.
[48] Milani AL, et al., Trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh: 1 year outcomes. Am J Obstet Gynecol 2011;204:74.e1-8.
[49] Maher C, et al., Surgical management of pelvic organ prolapse in women: a short version Cochrane review. Neurourol Urodyn. 2008;27(1):3-12.

improvement at one year.[50]

These results are consistent with similar prospective, multicenter studies reporting 1-year anatomic outcomes, ranging from 79-91%, after POP repair with the original polypropylene mesh in the Prolift system.[51] A decrease in the success rate of Prolift +M was observed after 3 months followup. These results are similar to the changes in outcome seen over time with Prolift.[52] Quemener and colleagues in 2014 reported their experience regarding the use of partially absorbable mesh in 269 consecutive patients who underwent Prolift +M.[53] At a median follow-up of 20 months the re-intervention rate was 8% (2% exposure, 1.2% recurrent prolapse, urinary incontinence 5%). These authors noted that in their own practice as well as their review of the literature, that "partially absorbable mesh does not seem to give advantages in comparison with classic non-absorbable mesh regarding rates of re-intervention." DeLandsheere and colleagues, in a retrospective study of 524 Prolift patients with a median follow-up duration of 38 months, observed a rate of mesh-related complications of 3.6%.[54]

Khandwala in 2011 assessed the safety, efficacy, and potential complications of Prolift +M system to correct uterovaginal prolapse in a prospective study of 167 women.[55] The anatomic success rate was 72.5%, the rate of perception of bulge was 4.4%, the rate of erosions was 3.6%, the rate of pain/dyspareunia was 3.7%, the rate of incontinence was 0.7%, the rate of de novo urge urinary incontinence was 8.7%, the rate of voiding dysfunction was 0.6%, the rate of recurrent urinary tract infection was 2.2%, and the rate of anal incontinence was 2.2%). This study demonstrated that Prolift +M was not superior to Prolift. In

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[50] Bhatia N, et al., A Comparison of Sexual Function Outcomes 1 Year After Undergoing a Transvaginal Mesh Procedure Using Polypropylene Mesh vs. Hybrid Polypropylene/Poliglecaprone Mesh. Female Pelvic Med & Reconstr. Surg 2012 Mar/Apr;18(2 Supp. 1), Oral Poster 19.

[51] Elmer C, et al., Trocar-Guided Transvaginal Mesh Repair of Pelvic Organ Prolapse. Obstet & Gynecol 2009 Jan;113(1):117-26; Milani AL, et al., Trocar-guided total tension-free vaginal mesh repair of post-hysterectomy vaginal vault prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Oct;20(10):1203–11.

[52] van Raalte HM, et al., One-year anatomic and quality-of-life outcomes after the Prolift procedure for treatment of posthysterectomy prolapse. Am J Obstet Gynecol 2008 Dec;199(6):694.e1-6.

[53] Quemener J, et al., Rate of re-interventions after transvaginal pelvic organ prolapse repair using partially absorbable mesh: 20 months median follow-up outcomes. Eur J Obstet Gynecol Reprod Biol. 2014;175:194–8.

[54] de Landsheere L, et al., Surgical intervention after transvaginal Prolift mesh repair: retrospective single-center study including 524 patients with 3 years' median follow-up. Am J Obstet Gynecol 2012;206:83.e1-7.

[55] Khandwala S and Jayachandran C, Transvaginal mesh surgery for pelvic organ prolapse—Prolift+M: a prospective clinical trial. Int Urogynecol J. 2011 Nov;22(11):1405-11.

2013 Khandwala reported in the subjective success of Prolift +M was 88.1%.[56]

In a prospective randomized multicenter trial, Farthmann and colleagues found rates of re-intervention for prolapse recurrence in partially absorbable mesh group and non-absorbable mesh group to be equal.[57] Lensen and colleagues found similar conclusions: the rates of anatomic failure, including the untreated compartments, were identical after Prolift and Prolift +M.[58] Re-intervention for mesh exposure of Prolift +M was around 2% and usually occurred between 4.7 and 7.5 months. Risk factors for mesh exposure, such as the T-incision or concomitant hysterectomy, are identified in the literature.[59] According to Withagen, surgeon experience is reported to be the utmost importance in avoiding mesh exposure and may explain the lower mesh exposure rate in the Quemener study.[60]

The Prolift +M absorbable lightweight mesh, while safe and effective, does not result in a lower mesh exposure rate compared to Prolift.[61] The safety profile was comparable to the original mesh repairs.[62] Lighter-weight mesh provides anatomic support consistent with the original polypropylene mesh, and demonstrates excellent functional improvements.

I share the same opinion of Milani, that is there is no difference in mesh exposure rates or dyspareunia rates between Prolift and Prolift +M. This is based on my review of the clinical data on the compatibility of Gynemesh PS and the Prolift +M mesh™, my review of the medical literature and my own personal

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[56] Khandwala S, Transvaginal Mesh Surgery for Pelvic Organ Prolapse: One-Year Outcome Analysis. Female Pelvic Med Reconstr Surg. 2013 Mar-Apr;19(2):84-9.

[57] Farthmann J, et al., Lower exposure rates of partially absorbable mesh compared to nonabsorbable mesh for cystocele treatment: 3-year follow-up of a prospective randomized trial. Int Urogynecol J 2013;24:749–58.

[58] Lensen EJ, et al., Comparison of two trocar-guided trans-vaginal mesh systems for repair of pelvic organ prolapse: a retrospective cohort study. Int Urogynecol J. 2013 Oct;24(10):1723–31.

[59] Collinet P, et al., Transvaginal mesh technique for pelvic organ prolapse repair: mesh exposure management and risk factors. Int Urogynecol J 2006;17:315-20.

[60] Withagen MI, et al., Trocar-Guided Mesh Compared With Conventional Vaginal Repair in Recurrent Prolapse. A Randomized Controlled Trial. Obstet Gynecol 2011 Feb;117(2 Pt 1):242–50; Quemener J, et al., Rate of re-interventions after transvaginal pelvic organ prolapse repair using partially absorbable mesh: 20 months median follow-up outcomes. Eur J Obstet Gynecol Reprod Biol. 2014;175:194–8.

[61] Milani AL, et al., Trocar-guided mesh repair of vaginal prolapse using partially absorbable mesh: 1 year outcomes. Am J Obstet Gynecol 2011;204:74.e1-8.

[62] Caquant F, et al., Safety of Trans Vaginal Mesh procedure: Retrospective study of 684 patients. J Obstet Gynaecol Res. 2008 Aug;34(4):449–56; Elmer C, et al., Trocar-Guided Transvaginal Mesh Repair of Pelvic Organ Prolapse. Obstet & Gynecol 2009 Jan;113(1):117-26; Milani AL, et al., Trocar-guided total tension-free vaginal mesh repair of post-hysterectomy vaginal vault prolapse. Int Urogynecol J Pelvic Floor Dysfunct. 2009 Oct;20(10):1203–11.

experience with these two kits. I feel both products are effective and suitable for use in prolapse repair as the recurrence rate is less than native tissue repairs and the dyspareunia rate no greater than native tissue repairs.

2. Benefits and Risks

Like all surgical techniques, the incorporation of mesh into surgical POP repair has potential advantages and disadvantages. Mesh may improve long-term anatomic results of surgery as compared to non-mesh repairs for some types of prolapse.[63] Like with all surgeries, complications such as erosion, pain, urinary tract injury, and sexual dysfunction may be due to surgical technique, the materials utilized, patient anatomy, or a combination of factors. It is also important to recognize these complications are not unique to mesh surgeries, and are known to occur with non-mesh-based repairs. There is no convincing evidence that transvaginal mesh can cause an autoimmune response, and there is no reason to remove vaginal mesh in asymptomatic patients. In patients who have had vaginal mesh surgery for POP and are satisfied with their results, there is no need to take any action other than routine check-ups and follow-up care.[64]

In some circumstances, transvaginal mesh for pelvic organ prolapse may be the most appropriate surgical option.[65] There are certain clinical situations where many would agree the use of transvaginal mesh is not only acceptable, but preferred. Examples of these clinical situations include: patients with recurrent prolapse after a non-mesh, native tissue repair; or patients in whom an abdominal approach may pose additional and potentially more significant surgical risks, such as patients with pulmonary co-morbidities or patients with known significant intra-abdominal adhesions. It is AUGS's "strong opinion . . . that there are subsets of women with prolapse, and in some cases those with the most advanced disease, in whom the benefits of transvaginal mesh outweigh the risks and a blanket ban on the use of these products compromises patient care."[66]

Prolift and Prolift +M provided many unique benefits to women, in that they had minimal recovery times, brief operative time, they were durable, had high success rates, and low complications rates.[67] The rates of pain and dyspareunia and changes in vaginal length and caliber were not significantly different than

[63] AUA Position Statement on the Use of Vaginal Mesh for the Repair of Pelvic Organ Prolapse, 2011.
[64] AUA Position Statement on the Use of Vaginal Mesh for the Repair of Pelvic Organ Prolapse, 2011.
[65] AUGS Position Statement on Restriction of Surgical Options for Pelvic Floor Disorders, 2013.
[66] AUGS Position Statement on Restriction of Surgical Options for Pelvic Floor Disorders, 2013.
[67] Benbouzid S, et al., Pelvic organ prolapse transvaginal repair by the Prolift system: Evaluation of efficacy and complications after a 4.5 years follow up. Int J Urol 2012;19:1010–1016.

those seen with non-mesh native tissue repairs. Contraction of tissue and dyspareunia are long-known risks of vaginal surgery.[68]

The risks specific to Prolift +M are identified in the IFU and Professional Education materials, and are well-known to surgeons who perform prolapse surgery. The most common risk is a graft-related complication, which is mesh exposure. Mesh exposure is warned of in the IFU. These exposures can be treated in most instances with excision of the exposed material. The outcome is usually good once the complication has been addressed appropriately. Long-term serious adverse mesh-related events are uncommon. Prolift +M has essentially the same risks factors and complications as other transvaginal repairs, such as traditional native tissue repairs or reinforced biological repairs that use a permanent suture for fixation. For instance, injury to surrounding structures such as the bladder, urethra, ureter, bowel, rectum, nerve, or vaginal wall resulting in a fistula, bleeding, infection, pelvic pain, or dyspareunia can occur from dissection in a native tissue repair, or from dissection in a Prolift case. Foreign body reaction, rejection, infection, exposure/erosion of synthetic material, and other wound complications can occur from a transvaginal native tissue repair or reinforced biological repair as well.

Tissue contraction is a potential risk well-known to surgeons who perform prolapse surgery. Vaginal tissue contracture, which is warned of in the Prolift +M IFU and in Professional Education materials, can occur from a native tissue repair, colporrhaphy, or Prolift +M. However, if Prolift +M is placed tension-free as described in the IFU and as can be seen in Professional Education materials, it is rarely clinically significant.

Prolift and Prolift +M was an important treatment option for many women with POP. For instance, women with weak tissue and/or severe forms of prolapse may especially benefit from a reinforced mesh repair. When Prolift and Prolift +M were available and I was having a conversation with a patient with an anterior/apical compartment prolapse about which procedure to choose, I would advise patients that some native tissue repairs have a low risk of re-operation for a foreign body complication, but a 40% risk of re-operation for recurrent POP. Conversely, if they chose Prolift +M, it would be rare that the POP would ever return in the treated compartment, but there would be a 5-15% risk of mesh-related complication leading to re-operation. After the surgeon makes a detailed consultation considering the history, physical, past medical and surgical history, the surgeon makes a recommendation on the approach that is best for that individual. The informed consent process that occurs between the surgeon and

[68] Francis WJA and Jeffcoate TNA, Dyspareunia Following Vaginal Operations. J Obstet Gynecol Br Commonwealth 1961 Feb;68(1):1–10.

patient should discuss the risks, benefits, and expected convalescence with each of the commonly performed repairs. Ultimately, the patient decides how to proceed, and if the surgeon agrees, then the operation is performed.

Many critics of the use of transvaginal mesh kits feel these procedures are never indicated. They favor abdominal sacrocolpopexy for all patients. However, there are many patients such as elderly patients that simply will not tolerate an abdominal approach due to co-morbid conditions. Abdominal sacrocolpopexy, even when performed laparoscopically, has significant peri-operative morbidity such as hemorrhage, bowel injury, and obstruction. It also can be difficult to perform in patients with multiple prior abdominal surgeries due to adhesions. It does not address rectocele very well, and can cause de novo stress urinary incontinence.[69] Moreover, there is a risk of suture and mesh exposure with sacrocolpopexy, and in a large study performed by the Pelvic Floor Disorders Network, the probability of mesh erosion was reported to be 10.5%. Like Prolift +M, this may require surgical treatment, and having to abdominally reoperate to treat these complications poses greater risks and morbidity to the patient. Critics may offer an obliterative transvaginal procedure known as colpocleisis in such patients. However, many elderly women, even if no longer sexually active, do not want an obliterative procedure that negatively affects body image.

3. Inflammation After Prolift +M and Claim of Cytotoxicity

Plaintiffs' experts have suggested that there may be an inappropriate inflammatory response with the Prolift +M. This has not been the case in my practice, nor is there any literature from peer-reviewed urology, urogynecology, or gynecology journals that have demonstrated this to be the case. (See studies referenced above, which do not support this. Professional statements do not support this.)

In the Performance section of the IFU, Ethicon informs physicians that the mesh elicits a minimum to mild inflammatory reaction. From a physician's standpoint, I am concerned about a persistent acute inflammatory response that has a clinical effect on patients. The Ethicon IFU tells me that there will be an inflammatory response to insure the tissue integrates into the mesh, and that this inflammatory reaction is minimum to mild. On a microscopic level, there will be a minimal-to-mild chronic inflammatory response, but as this has no clinical effect on patients, it is not a concern for me or any other reasonable physician. This section properly tells physicians about the clinical implications of the inflammatory response. It also tells physicians that the tissue will incorporate into the mesh; therefore, if removal is necessary, it is explicit that you will have to cut

[69] Nygaard I, et al., Long-term Outcomes Following Abdominal Sacrocolpopexy for Pelvic Organ Prolapse. J Am Med Assoc 2013 May;309(19):2016–2024.

around the tissue to explant the mesh. This tells a pelvic floor surgeon exactly what would be necessary to remove the mesh and the implications for the patient.

4. Claims of Degradation After Prolift +M

Clinical evidence does not show that the Prolift +M mesh degrades or that if it did it leads to a clinically significant effect. The clinical studies discussed above show lasting success, low late-term complications, and are inconsistent with this degradation theory. Studies like Clavé 2010[70] do not account for handling and alteration during processing prior to analysis. Clavé 2010 is unreliable and fails to show degradation PP. The sample analyzed in that study was less than 1/3 of the overall cohort (32 out of 100) and no selection criteria was described. The authors also failed to discuss whether any damage to the mesh occurred during surgical explantation. The SEMs showing surface cracking could be from biologic material and handling, as well as preservation.

Moreover, the chemical analyses performed do not show degradation. Likewise, the Costello study[71] sometimes relied upon by plaintiffs' experts was a case report, which is unreliable and concerned a Bard mesh. One must also remember that biologic materials, as well as autologous and cadaveric fascia are known to degrade.[72]

From a clinical standpoint, I have never seen the Prolift +M mesh degrade or cause any clinical effect. I have not witnessed any gross evidence of mesh degradation on surgical revision cases. If somehow the mesh did microscopically degrade, there has been no clinical effect. Moreover, I have never read or seen a single peer-reviewed published article (or seen any cited by plaintiffs' experts) that showed any clinical effect of degradation. Finally, the study by Clavé did not evaluate PP/PG constructs; rather, he looked at only one composite mesh PP/PGA (Vypro). Claims of polypropylene degradation based on the Clavé study are therefore not supported by this study.

5. Claims of Cancer After Prolift +M

There is no reliable scientific information to support the claim that polypropylene can cause cancer or sarcoma. I have not personally witnessed cancer from mesh in any patient that I have implanted with polypropylene in 15 years, and after more than 1,000 surgical implants. My experience is consistent

[70] Clavé A, et al., Polypropylene as a reinforcement in pelvic surgery is not inert: comparative analysis of 100 explants. Int Urogynecol J 2010;21:261–270.
[71] Costello CR, et al., Characterization of Heavyweight and Lightweight Polypropylene Prosthetic Mesh Explants From a Single Patient. Surgical Innovation 2007;14(3):168–176.
[72] Woodruff A, et al., Histologic Comparison of Pubovaginal Sling Graft Materials: A Comparative Study. Urology 2008;72:85–89.

with the clinical literature.[73] Moreover, the scientific data does not support plaintiffs' experts' contention that the Prolift +M presents a risk of sarcomas or cancer. There are no reports in the medical literature of tumors related to the implantation of surgical-grade polypropylene for midurethral slings or prolapse mesh kits, and there is no evidence suggesting any carcinogenicity in humans related to polypropylene despite hundreds of millions of individuals being implanted with the material in various forms for well-over a half century.[74] The Prolene material that the Prolift +M mesh is comprised of has been used for decades, and studies do not show a statistically significant risk of cancer. There was no need for Ethicon to warn of this alleged risk in the Prolift +M IFU.[75]

IV. Prolift +M™ Instructions for Use (IFU)

A. Product Description, Warnings and Adverse Reactions

Ethicon's IFU for Prolift +M properly provides the indications for use, contraindications, warnings, and adverse reactions. The adverse reactions section in the IFU properly warns of the complications that are associated with the mesh, and the tools for implementing the mesh in Prolift +M. It warns of the only unique complication with the device—mesh exposure, erosion, or extrusion. Although as noted above, suture exposure and other wound complications can occur with non-mesh prolapse repairs.

When Ethicon or any corporation drafts an IFU, its intended audience is the physician. Importantly, the IFU provides that "*[u]sers should be familiar with surgical procedures and techniques involving pelvic floor repair and synthetic meshes before employing the Gynecare Prolift +M™ Systems.*" "*Acceptable surgical practices should be followed for the Gynecare Prolift+M™ Systems as well as for the management of infected or contaminated wounds. If the Mesh*

[73] King AB, et al. Is there an association between polypropylene midurethral slings and malignancy? Urology. 2014 Oct;84(4):789-92; King AB, Goldman HB. Current controversies regarding oncologic risk associated with polypropylene midurethral slings. Curr Urol Rep. 2014 Nov;15(11):453.

[74] AUGS & SUFU, Frequently Asked Questions by Providers—Mid-urethral Slings for Stress Urinary Incontinence. (available at http://www.augs.org/p/bl/et/blogaid=194); Dwyer PL and Riss P, Carcinogenicity of implanted synthetic grafts and devices. Int Urogynecol J 2014 May;25(5):567–568.

[75] Moalli P, et al., Polypropylene mesh: evidence for lack of carcinogenicity. Int Urogynecol J 2014, DOI 10.1007/s00192-014-2343-8; King A, et al, Current Controversies Regarding Oncologic Risk Associated with Polypropylene Midurethral Slings. Curr Urol Rep 2014;15:453; Sunoco MSDS; AUGS & SUFU, Frequently Asked Questions by Providers—Mid-urethral Slings for Stress Urinary Incontinence. (available at http://www.augs.org/p/bl/et/blogaid=194); Linder BJ, et al., Evaluation of the local carcinogenic potential of mesh used in the treatment of female stress urinary incontinence. Int Urogynecol J 2016 DOI:10.1007/s00192-016-2961-4.

Implant is used in contaminated areas it must only be with the understanding that subsequent infection may require its removal." This is very important, because physicians who have this type of experience are knowledgeable of the anatomy, complications, and how to handle complications.

The IFU further warns: "Potential adverse reactions are those typically associated with surgery employing implantable materials of this type, including hematoma, urinary incontinence, urinary retention/obstruction, ureter obstruction, voiding dysfunction, pain, infection potentiation, wound dehiscence, nerve damage, recurrent prolapse, inflammation, adhesion formation, fistula formation, contracture, scarring, and mesh exposure, erosion, or extrusion." It also warns that "[p]otential adverse reactions are those typically associated with pelvic organ prolapse repair procedures, including pelvic pain or pain with intercourse. These may resolve with time." The IFU also warns that "[d]issection for pelvic floor repair procedures has the potential to impair normal voiding for a variable length of time."

Further, the IFU states that scarring, infection, contracture, erosion, and nerve injury can take place, which would obviously result in pelvic pain and pain with sexual intercourse. All pelvic floor surgeons know this based upon their common and basic surgical knowledge. Ethicon is responsible for identifying the complications, but not the implications of each complication; otherwise the IFU would become a treatise.

Furthermore, it is not necessary to identify patient selection factors any further than Ethicon did. Ethicon identified its indications for use and the contraindications. All areas in between are to be determined by the patient and physician.

Some physicians state that mesh should only be used for recurrent prolapse. This is not the case, and is not supported by the data. This is a decision that a physician and patient must make together, as there are forms of severe prolapse for which a transvaginal mesh would be useful. Further, some physicians state transvaginal mesh may not be used on younger sexually active women. This statement is not supported by data, and therefore I disagree with the statement that it should have been in the IFU. Only the patients and physicians together may determine if its use on a young sexually active patient is appropriate. For instance, in a young sexually active woman with weak tissue, it may be likely that a native tissue repair would fail and necessitate a secondary repair. And there are no statistically significant differences in the rates of pain, de novo dyspareunia, or changes in vaginal caliber and length when one examines the randomized controlled trials comparing Prolift or Prolift +M to native tissue repair. Therefore,

the surgeon may recommend a more durable repair such as Prolift +M even where the patient is not suffering from recurrent prolapse.

V. Prolift Monograph

The IFU is a comprehensive document overviewing total pelvic floor repair, anterior pelvic floor repair, and posterior pelvic floor repair. Important principles of the procedure, product description, preoperative preparation, and patient positioning are included, as well as a discussion of a potentially higher-risk of mesh erosion with concomitant hysterectomy, as seen by the TVM Group. The document reviews the contents of the kit (Guide, cannula, retrieval device, anterior implant, posterior implant, and total implant).

The surgical technique guide for physicians contains general guidelines, and is not a substitute for training and experience. The physician is to take these general guidelines along with using his skill to see how these guidelines apply to the individual patients' anatomy.

Critics have stated that more information should be provided on how to trim the mesh. The IFU states that physicians are to be familiar with pelvic floor repair with meshes, and such physicians are to know how to trim the mesh appropriately for their patient. A guideline cannot outline the individual anatomy for each patient. Further, such physicians must know how and where to place such meshes appropriate for their patients, and to be able to place items tension-free.

In 2007, Ethicon produced and began distributing the Prolift Surgeon's Resource Monograph at professional education events and other meetings. This monograph provides a unique opportunity for surgeons have access to the experience of pelvic surgeons from around the world who have performed a large number of Prolift Pelvic Floor Repair System procedures. The document was an open exchange of ideas representing the most up-to-date information possible. The perspective that must be kept in mind was that it was information that was not available on most procedures. All surgical procedures have complications, and experience-related consequences are seen in even the most basic urogynecologic surgeries. This monograph was published after 35,000 Prolift procedures worldwide. The report is a summary of the collective experiences of the most experienced Prolift users who were invited to attend one of five Prolift user forums held throughout the world. The comments and opinions contained within the document represent the experiences of the ten authors, as well as over 200 participating international prolapse surgeons.

The monograph provided expert opinions on the use of the Prolift (Total, Anterior, and Posterior) Pelvic Floor System. There are fifteen sections:

Introduction, patient selection, preparation, surgical technique, anesthesia and hydrodissection, incisions, additional sutures, mesh handling, complications, hemorrhage, visceral injury, infection, mesh complications (erosion, exposure, and extrusion), dyspareunia and vaginal pain, clinical data summary, and appendix. Each section provides personal insight from some of the most experienced pelvic surgeons in the world. In my opinion, the monograph is the most comprehensive, detailed, practical document on a single pelvic surgery I have read in my career. The document is not meant to replace the surgeon's thoughts and skills obtained in medical school, residency, fellowship, and practice, as these attributes are irreplaceable. Rather, the monograph provided feedback from some of busiest pelvic surgeons in the world on a procedure used to repair prolapse on more 35,000 women at the time of publication.

Plaintiff's experts will argue that the monograph should have been provided at the launch of the procedure. This of course would not have been possible; as such insight is only gained through introduction, development, and extensive utilization of a procedure. The monograph did provide meaningful feedback to less experienced surgeons around the world, and it advised of device use as well as complications and their management.

The same TVM group that published their data on Prolift and the Prolift Monograph had similar experience with Prolift +M. Although, they did not create a specific monograph for Prolift +M, the Prolift monograph developed by the TVM group can still be used to educate surgeons on Prolift +M surgical technique. The small differences in the mesh design do not change the important surgical principles outlined in the Prolift monograph, including patient selection, preoperative preparation, patient positioning, trocar placement and mesh deployment. Finally, the Prolift monograph review of the kit (Guide, cannula, retrieval device, anterior implant, posterior implant, and total implant) may be applied to the Prolift +M kit.

VI. Prolift +M™ Patient Brochures

I have reviewed the 2009 patient brochure. The purpose of the patient brochure is to facilitate a conversation with the patient and the physician. All the brochure properly identifies is the disease state, options for women, and the complications. And most importantly, the brochures tell women that this surgery should be performed only after a complete physical examination.

The brochure reviews what pelvic organ prolapse is, what the symptoms are, how it is diagnosed, and how it is treated. The brochure reviews surgical procedures for POP. It describes the product Prolift +M and how it is different from other surgical procedures. The brochure describes how Prolift +M works,

how long the surgery takes, and the expected convalescence. The brochure states the all surgical procedures have some risks. *"Although rare, complications associated with the procedure include injury to blood vessels of the pelvis, nerve damage, difficulty urinating, bladder and bowel injury. There is also a small risk of the mesh material becoming exposed into the vaginal canal."* It mentions only a complete physical exam and consultation with the physician can determine which procedure is right for you.

With regard to the brochure, it is my opinion that describing the perioperative complications as "rare" is correct, and that erosion rates are small compared to the large number of patients—85 to 95% of whom do not have erosions. Further, the inclusion of pain or pain with sexual intercourse is not necessary, and would not elicit a conversation that would not already be elicited by the complications identified in the patient brochure, the IFU, and the physician's surgical knowledge, as all surgical options to treat prolapse carry this risk, and the risk is no higher with Prolift +M. It must be understood that the patient brochure is not designed to identify all complications, but to facilitate a conversation with the physician so that the physician can discuss the complications and rates based upon his/her practice and the individual characteristics of the patient.

The Prolift +M brochure mentions the risk of scarring, pain during intercourse, or pain for the partner. It mentions that exposure of the mesh may require surgical removal. The brochure mentions that synthetic mesh is a permanent medical device implant. *"Therefore, you should carefully discuss the decision to have surgery with your doctor and understand the benefits and risks of mesh implant surgery before deciding to how to treat your condition."*

The patient brochure serves to merely introduce the Prolift +M device. It is not intended in any way to substitute for a consultation and informed consent with their pelvic surgeon. It is the surgeon's job to inform the patient of the risks and benefits of the procedure. It is the surgeon's responsibility to answer the patient's questions and decide if the patient is an appropriate candidate for Prolift +M after discussing the risks, benefits, and alternatives.

VII. Ethicon Professional Education on Prolift +M™

A. Introduction

The Prolift +M IFU recommends that surgeons attend professional education. Thus, in my opinion, the Ethicon Professional Education Program supplements the IFU. I became familiar with the Ethicon Professional Education Program when I attended a course on the TVT-O in San Francisco on March 23,

2004. This was a didactic session at a hotel near the San Francisco airport. The course faculty overviewed the proper patient selection, indications for the procedure, and surgical dissection. Afterwards, there was a laboratory session at a nearby facility where physicians were instructed on how to use the device on a cadaver. This was a hands-on laboratory session, where experts on the procedure who were preceptors for Ethicon instructed physicians. The preceptors guided the new users on how to properly perform the procedure. In December of 2004, I became a preceptor for Ethicon on the TVT™ procedure.

I attended a course on the Prolift in Milwaukee, WI in 2005. This was a proctorship that Dr. Dennis Miller directed. Dr. Miller overviewed the proper patient selection, indications for the procedure, and surgical dissection. In 2006, I became a preceptor on Prolift™ and Prolift +M™ when it became available to me in March 2009.

I functioned as a preceptor for Ethicon from 2004 until 2011. I have personally instructed physicians on how to perform the TVT™ procedure, TVT Obturator,™ TVT Secur,™ TVT Abbrevo,™ TVT Exact™ as well as Prolift™ and Prolift +M.™

B. Phases of Professional Education Program

Ethicon Professional Education Program involves three phases. The first phase is a preceptorship where physicians will attend a course with the designated topic of incontinence, prolapse, or occasionally both. This will include 3-4 hours of didactics overviewing patient selection, surgical technique, and long-term data on the device. The second half of the day is spent in a hands-on cadaver lab. Another form of education is direct observation in the operating room, where surgeons will be invited into the OR and will watch an experienced surgeon perform the Prolift +M™ or TVT™ procedure. The third phase of education would be a proctorship, where the preceptor for Ethicon would be a guest in another surgeon's institution and directly observe them performing the TVT™ or Prolift +M™ procedure to serve as a reference on how to properly use the surgical kit provided by Ethicon.

After having participated in the Ethicon Professional Education Program for eight years both as an attendee and as a preceptor, I feel that the program has high ethical standards and there was no pressure from the company to convince attendees that their products could be placed without preexisting knowledge of pelvic anatomy. The courses were provided to help educate the physician on how to use the kit properly and to practice on a cadaver. The preceptorships allow new users to witness experts placing the device. Proctorships provide an opportunity for new users to have their initial cases observed by an expert.

C. Complication Prevention and Management

The professional education department actively worked on how to prevent and manage complications. The group included senior Ethicon staff. The Ethicon USA and worldwide product manager, research and development staff, medical director, and professional education managers were among members of the panel. The physicians on the panel were preceptors that had a vast personal experience with pelvic reconstructive surgery and intimate knowledge of the Prolift +M™ system.

There was a continuous and collaborative effort to identify and implement ways to avoid complications. There was review of how and why complications occur. At bi-annual meetings and summits, the education panel would receive information on complications, and then provide feedback to Prolift +M™ users on how to prevent these complications. The group also made presentations on complications and algorithms to manage adverse events. This allowed for improvement in surgical techniques and helped better identify who was an appropriate candidate for the procedure. There was significant education provided on how to recognize and treat mesh-related complications such as exposure, erosion, and pain.

Preceptors and Ethicon professional education staff were available to their trainees to discuss complications and provide advice on how to effectively manage complications. This close network allowed rapid bi-directional feedback from the company to the physicians.

Preceptors recommend using the following techniques to avoid complications associated with Prolift +M™: (1) performing an initial full-thickness vaginal wall dissection, (2) placement of the mesh graft in a tension-free fashion, (3) avoiding trimming of the vaginal epithelium, and (4) proper postoperative follow-up to ascertain whether long-term complications have developed.

E. Credentialing

The Ethicon Profession Education Program is not a credentialing process. Ethicon did provide a certificate noting that a surgeon did attend their course on a particular product like Prolift +M. But this certificate by no means verifies that the physician is proficient at performing the procedure.

The certificate from the program simply documents the surgeon's attendance at an Ethicon Professional Education Event. It shows that the physician made an attempt to be educated on the procedure and Ethicon's efforts

to provide exposure to their products. The actual credentialing should always occur at the hospital level and is up to the physicians on the committee to decide which procedures the surgeon is capable of performing. It is the physician's responsibility to know the pelvic anatomy, understand biomaterials, and properly select patients for the procedure. Prolift +M is merely a kit to help the surgeon place a mesh graft in the vagina using a trocar system for anchoring that decreases the amount of dissection required and allows a reliable anchoring mechanism for the graft. The Prolift +M system does not in any way make the surgeon competent in anatomy, proper dissection, tunneling, graft deployment, and wound closure. AUGS has recently issued a credentialing recommendation regarding transvaginal and abdominal prolapse mesh usage. Many of the recommendations for ways that a surgeon could gain further knowledge were encompassed years ago, beginning in 2005, by the Prolift and 2009 by the Prolift +M professional education program. The materials were then and are today state of the art. The importance of these materials was set forth in the IFU, which advised surgeons of their existence and recommended that they take the opportunity to receive professional education. This education included models, surgical videos, cadaver labs, proctoring, handouts and other information that was more than adequate and very helpful.

VIII. Product Design

A. The Usefulness and Desirability of the Product

Prolift +M has a number of useful and desirable features. Prolift +M is a type 1 large-pore-size polypropylene mesh. The trocar system is unique in that it offers a minimally invasive approach for graft augmentation in prolapse surgery. The trocar allows the surgeon to suspend the vagina to deep structures, including the sacrospinous ligament, that are often difficult to access with traditional fixation techniques such as suturing. This is a desirable feature for surgeons when performing prolapse surgery, as it allows for an improved prolapse outcome due to the improved reduction of the prolapse when compared to native tissue repair.

The utility of this product to the surgeon and to the public is that it allows the surgeon to place polypropylene mesh via a vaginal incision using a minimally invasive approach. Patients with recurrent prolapse especially benefit from a transvaginal polypropylene mesh placed with trocars. Moreover, there are many patients that are not appropriate candidates for mesh placement using an abdominal approach due to comorbid conditions such as abdominal adhesions, morbid obesity, and pulmonary disease. Patients with pulmonary disease or morbid obesity do not tolerate laparoscopic surgery very well. The steep Trendelenburg position and the CO_2 insufflation required in laparoscopic and robotic surgery impair mechanical ventilation and hence oxygenation. This often prohibits laparoscopic and robotic surgery. Also, patients with abdominal

adhesions are at risk for bowel injury from a laparoscopic trocar or from the dissection in an open abdominal approach. These distinct and common patient populations certainly benefit from a vaginal approach as it obviates the need for Trendelenburg, CO_2 insufflation, and lysis of abdominal adhesions. Its standardized nature allowed the mass accumulation of clinical data that could be assessed including level 1 studies and trials across the various countries. Before Prolift and Prolift +M there were many POP procedures that have been studied far less yet were in practice, with many existing for decades without RCTs, as compared to Gynemesh PS and Prolift, which were quickly assessed in RCTs according to practice in the POP field. This is another feature that makes the design state of the art, ahead of prior practice, desirable, and useful.

B. The Safety of the Product

Prolift +M is a safe product that is no more likely to cause injury to surrounding structures such as the bladder, ureter, rectum, or nerves than traditional native tissue repair. All prolapse surgeries—including native tissue repair—can cause bleeding, infection, pain, and dyspareunia. None of these complications are unique to transvaginal mesh kits such as Prolift +M.

There are graft-related complications when using augmentation—either biological or synthetic grafts, or synthetic sutures. Any foreign body has the potential for graft exposure that may need surgical treatment. These well-recognized safety concerns, which were taught to surgeons in basic training and discussed in the medical literature and at conferences well before Prolift +M, are not unique to Prolift +M. These potential risks are obvious to the surgeon. The kit was designed with a narrow trocar and a surrounding plastic sheath with a lightweight, large-pore-size mesh. These features result in a favorable safety profile.

The severity of complications from the Prolift +M kit is usually minor. In fact, the most common complication is vaginal mesh exposure. Graft exposure can usually be managed with minor surgical excision, and usually does not require multiple operations. Some patients are also managed medically with success, as reflected in the clinical literature.

Many of the sexual side effects that occur after prolapse surgery are related to the concomitant hysterectomy or oophorectomy. Specifically, oophorectomy leads to menopause. The post-menopausal symptoms such as anorgasmia and decreased libido are a direct result of menopause. These symptoms are often incorrectly attributed to prolapse surgery or the mesh graft. The risks of vaginal and prolapse surgery to lead to tissue contraction, pain, and dyspareunia were also

well known, taught, and discussed in the literature and other venues long before Prolift +M. These potential risks are obvious to the surgeon.

Pelvic surgeons, investigators, and industry have been interested in using graft material to augment surgical repair of prolapse in efforts to improve the outcome when compared to native tissue repairs. The search for the ideal graft material in prolapse surgery has evolved over the past 25 years. The results have shown that Gynemesh PS has the best balance of graft characteristics when compared to FDA-approved alternatives.

Current options for graft augmentation when performing prolapse surgery include allografts, xenografts, and synthetic materials such as polypropylene mesh. Allograft material such as cadaveric skin or fascia has been used in prolapse surgery for many years. However, allograft strength weakens with time, leading to a failed repair. Moreover, not unlike polypropylene, these grafts can become exposed postoperatively. Many patients, including Jehovah's Witnesses and Native Americans, refuse tissue transfer from the deceased. Also, many patients have strong reservations about disease transmission with soft-tissue allografts. Xenografts offer an alternative to allografts and are less expensive and more readily available. Xenografts avoid the risk of disease transmission and cultural concerns of using cadaveric tissue, but can lead to an immune reaction leading to tissue rejection, extrusion, and other healing abnormalities. Bovine products have largely replaced porcine grafts. However, unlike Prolift +M, the medical literature regarding safety and efficacy of bovine grafts is scarce.

Prolift +M mesh does not transmit disease, does not cause an immune reaction, is less expensive than allografts and xenografts, and is widely familiar and accepted by the public. Surgeons and the public are familiar and have widely accepted polypropylene mesh for use in hernia and incontinence surgery. Consequently, it is not surprising that pelvic surgeons prefer polypropylene. It is lightweight and has large-pore size that allows tissue compatibility. These mesh design features allow for tissue incorporation while incurring an expected level of native tissue reaction. Post monocryl absorption the graft maintains its architecture and anisotropic properties.

Some have argued that polypropylene mesh grafts for prolapse surgery can have an even greater pore size and be even lighter in weight. However, at some point the ultra-lightweight graft material will no longer support the prolapse, and the outcome will then approximate that of native tissue repair. This is a direct result of pore sizes that are too large, and fibers that are too thin to support pelvic organs. The mesh will eventually break, resulting in a failed operation.

The expected outcome of ultra-lightweight polypropylene grafts is reduced efficacy or durability when compared to Prolift +M. The ultra-lightweight mesh would not eliminate the added time, expense, and graft-related risks when compared to native tissue repair. In the use of Ultrapro in the Prolift +M device, resulted in a similar incidence of mesh exposure rates and dyspareunia when compared to Prolift. There is much more data on Prolift given its long-term use, which shows it is safe and effective. A larger pore lighter weight mesh—Vypro—was tried by the TVM Group, but it had many complications and was found not suitable for use in the pelvic floor repairs.

Avoiding danger by the exercise of care in the use of the Prolift +M is readily achievable and is primarily the responsibility of the surgeon. In order to avoid danger in pelvic surgery, the surgeon needs to have the proper medical school education, residency training, and experience in clinical practice. The surgeon should be extremely knowledgeable with pelvic anatomy in order to avoid complications inherent to pelvic surgery. Once the surgeon has a fundamental knowledge of pelvic surgery, he/she can then exercise care in the use of the mesh kit. In order to exercise care in the use of a mesh kit, the surgeon should become keenly familiar with the kit's Instructions for Use (IFU), which is included in the surgical packaging. Also, Prolift +M surgeons should become intimately familiar with the Prolift monograph, attend professional education events as recommended, and network with colleagues to allow an understanding of the product and the capacity to exercise care in placement of a transvaginal mesh kit.

The Prolift monograph, professional education events, cadaver labs, video and PowerPoint presentations, and close discussion with experts in pelvic surgery are important educational formats that are readily available to the surgeon.

Responsible pelvic floor surgeons would be aware of the potential complications involved with the use of the Prolift +M device due to their medical education, residency training fellowship training if any, and clinical experience. They would be aware of the potential complications involved with the use of the Prolift +M device due to the obvious characteristics of the device, with its trocars, mesh, and routes of placement, given decades of knowledge, reporting, and literature on prolapse surgical instruments, the surgical routes, and the use of mesh as earlier described. It is known and obvious that the use of trocars or any surgical instruments passing through the pelvis can cause injury. Trocars and surgical instruments had been in use long before Prolift +M, and were frequently employed in other procedures like laparoscopic surgeries as well. It is obvious to a surgeon that incisions and transvaginal surgery to correct prolapse can lead to pain and dyspareunia. It is also obvious and well-known that tissue contracts after surgery, that wound complications, delayed healing, and graft complications are a risk. Moreover, responsible pelvic floor surgeons would be aware of the potential

complications involved with the use of the Prolift +M device due to any product-specific training they have undertaken, their review of pertinent medical literature, and their review of the Prolift monograph and IFU, which also make these risks obvious.

Additionally, having had experience with traditional native tissue repair should provide the surgeon with the awareness of the pelvic anatomy and prolapse surgery and its attendant risks. Experience from using polypropylene mesh and trocars during stress urinary incontinence surgery and prolapse surgery will also serve as a foundation for the understanding of the inherent risks of a transvaginal mesh kit.

The Instructions for Use (IFU) also serves as a guideline for the surgeon. It provides detailed instructions for the surgeon. Also, it serves as a suitable warning for surgeons and information on proper patient selection. However, the IFU, Professional education, and Prolift monograph are never a substitute for the surgeon's knowledge of pelvic anatomy or surgical training and skill. Rather, those materials would be expected to comprise a small portion of the surgeon's overall level of awareness of the dangers of surgical products and Prolift +M's proper application and use.

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